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von Willebrand factor and angiopoietin-2: Toward an acute lung injury endothelial endophenotype?*

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Acute lung injury (ALI) continues to inflict a substantial toll on patients in our intensive care units. Although recent multicenter interventional trials report a steady decrease in control group mortality when low stretch ventilation and volume conservative therapies are instituted (1), mortality in ALI has remained much higher in observational studies (2–4). To date, identification of effective and specific ALI therapies has been elusive. The drive to maximize enrollment in ALI trials may have paradoxically hindered the ability to detect an effective therapy by inclusion of subjects with low baseline mortality rates. This effect was particularly apparent in the recently published omega-3 fatty acid and aerosolized b2-agonist interventional trials, in which adjusted control group mortality rates were <20% (1, 5). By focusing clinical trials to subjects predicted to be at high risk for mortality at the time of enrollment, investigators may be better poised to detect an effective therapy for acute respiratory distress syndrome. Furthermore, identification of plasma markers that associate with mortality may offer mechanistic insight about both the process of lung injury in general as well as a given patient's individual risk for lung injury, generating knowledge which may one day be harnessed for more personalized therapies.

Viewed in this context, the current *Critical Care Medicine* article by Calfee and colleagues (6) represents an important contribution to the field. The authors tested two potential markers of endothelial injury, von Willebrand factor (vWF) and angiopoietin-2 (Ang2), for an association with mortality in the National Heart, Lung, and Blood Institute's Fluid and Catheter Treatment Trial (FACTT) (7, 8). To address the goal of risk prediction, the investigators evaluated baseline levels, levels on day 3, and changes in levels between these time points. Baseline levels of both markers were associated with hospital mortality, but the association of Ang2 was significantly modified by the precipitating cause of ALI. In noninfected subjects, baseline Ang2 levels were highly associated with mortality. In contrast, among patients with either sepsis or pneumonia, which described 70% of the study population, baseline Ang2 levels were significantly higher than in noninfected subjects, yet the stronger associations with mortality were noted for day 3 levels or for the changes in

*See also p. 1731.

levels over time. Consistent with previous studies, baseline plasma vWF strongly associated with mortality and ventilator-free days. Examining the effect of volume-conservative therapy, the authors also demonstrated that Ang2 levels, but not vWF, were significantly reduced by a volume-conservative therapy in infected patients.

The results of the article by Calfee and colleagues raise several new questions about ALI pathogenesis. The lack of apparent association between mortality and baseline Ang2 among infected subjects is discordant with three other smaller trials (9–11). As the authors point out, the previous studies differ significantly from Fluid and Catheter Treatment Trial in the timing of plasma collection and in selection of patient populations. Furthermore, it is clear that among patients with sepsis, the variation in baseline Ang2 level is profound, with the highest quartile of patients exceeding ten-fold the median levels (6, 9–11). As common genetic variants in the Ang-2 gene associate with ALI susceptibility (12, 13), individual variation in the Ang-2 axis as patients respond to infection may in part account for this variability. Our group also found the genetic ALI susceptibility factor to associate with an apparent shift in the Ang2 isoform ratio (12), although there is no information on Ang2 isoforms in the Fluid and Catheter Treatment Trial population, and very little is known about whether Ang2 isoform specificity influences permeability. The Ang2—mortality relationship may also be modified by the plasma or lung levels of additional pathway members of the angiopoietin family, including the barrier enhancing molecule angiopoietin 1 (Ang1) or vascular endothelial growth factor, which may alter the action of ANG2 on its receptor (14), or by the receptor itself, tyrosine kinase with Ig and EGF homology domains-2 (TIE2).

The findings that changes in Ang2 levels tracked with outcomes, and are modified by volume strategy, may indicate that Ang2 is a pertinent marker of therapy response. The reversal of endothelial permeability, independent of inflammation, may be a novel therapeutic paradigm in sepsis and ALI (15). Animal studies in sepsis and lung injury have shown better survival with recombinant Ang1 or a synthetic TIE2 receptor agonist, and it seems likely that agents designed to modify the Ang–TIE axis may soon be available for clinical trials in critically ill populations (16–18). While agents blocking both Ang1 and Ang2 are in development for cancer therapeutics, it seems more appropriate to enhance Ang1 effects for sepsis or ALI. It will be important to test whether genotype or baseline Ang2 levels identify patients likely to benefit from such therapy and whether plasma Ang2 can serve as a monitor of response.

The apparent uncoupling of effects for vWF and Ang2 in the study by Calfee and colleagues should prompt further study on factors driving the expression, synthesis, storage, release, and plasma clearance of both vWF and Ang2. Notably, plasma vWF was not altered by low stretch ventilation strategy despite being a strong predictor of mortality, and some have suggested that the clearance of vWF is altered in critically ill patients who may not synthesize adequate ADAMTS-13 (a disintegrin and metalloproteinase with thrombospondin motifs 13) (19). It may also be that platelets are a more important source of plasma vWF than is currently appreciated.

Although neither plasma Ang2 nor vWF is a perfect ALI biomarker, both seem to have a role in identifying patients at higher risk for prolonged ventilation and death. In future studies, it will be important to validate the incremental predictive properties of these markers to assess clinical utility in broader populations. Further, to characterize a potential vascular injury endophenotype of ALI, future investigations could test whether these presumed endothelial factors associate with other relevant variables such as pulmonary dead space fraction, and whether they help to define ALI subjects in whom therapies to enhance vascular barrier function might be effective. Equally important will be the characterization

of patients in whom these markers fail to inform about mortality; when a patient with low baseline vWF and Ang2 levels dies from acute respiratory distress syndrome, was this a patient with a fundamentally different pathophysiology? As we build on the findings of Calfee and colleagues, future ALI investigations may find success by enriching their study population for such ALI subtypes at the outset.

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